

## Brain Stimulation Technology in Addiction Medicine; Main Problems Waiting for Solutions

The abuse of psychotropic drugs and addiction to them is an undeniable health issue. Based on United Nation reports, 185 million individuals across the globe are afflicted with illicit drug abuse. Considering the 2 billion alcohol consumers and at least one billion cigarette smokers, the need to conduct further studies and designing more effective treatments is even more apparent and considered as a national and international priority.

Despite this crucial importance, appropriate treatments for many types of dependencies on various substances are yet to be discovered; also, favourable outputs of accepted treatments have not been significant in the long run. In addition to the interference of different environmental factors in the initiation and continuation of addiction, the complexity of the biological aspects of this illness, is the main culprit of this treatment failure. Different brain areas involved in different dimensions of this illness and different chemical substances present in processes involved in substance abuse complicate the execution of therapeutic interventions. Even though pharmacological treatments for addiction have had promising outcomes, their nonspecific effects on different receptors and the impossibility of local intervention in targeted areas in the brain, has slowed down their advancement in the treatment of addiction.

Behavioural addictions such as pathological gambling, sex addiction or even internet addiction, habit problems such as obesity, compulsive and impulsive psychiatric disorders such as obsessive compulsive disorder and intermittent explosive disorder have shared neurocircuits with drug addiction and common problems and concerns in treatment. Therefore, any progress in a better understanding about drug abuse and addiction will help for developing a general multifactorial and explanatory model which improves the quality of existing therapeutic approaches and prevention strategies for all of these behavioural disorders and allows a clear classification on the basis of psychopathological and neurobiological insights.

Considering the presence of both biochemical and bioelectrical elements together in the nervous system, a goal oriented electrical intervention in cerebral functions along with chemical interventions via drugs, has been considered as a theoretical possibility for years. In 1985 Anthony Barker and Reza Jalinous showed that location oriented electrical stimulation could be carried out in the brain, using alternating magnetic fields outside the skull. On this basis the method of "electrical cortical stimulation using localized alternating magnetic field over the scalp" or Transcranial Magnetic Stimulation (TMS) was introduced. In 1990 Alvaro Pascual-Leone showed that more long-lasting effects could be achieved through repetitive TMS pulses (rTMS). For the first time in 1995, Mark George used rTMS as a therapeutic means in the treatment of depression, and hence the dream of applying electrical stimulation in the brain with no need for open surgery and skull dissection

was gradually realized. More extensive applications of this technology have been steadily discovered since 1998-1999, when the first reports on the safe dosage in humans were published. The first studies in the field of substance abuse commenced in 2003 with reports of successful studies by "Juhan et al. and Ishhmer et al"., and a new prospect was opened for the employment of this new technology in understanding and treating this disorder.

### Problems Awaiting Solutions

There are significant questions and major limitations in areas of understanding the pathophysiology (course of the illness) and the treatment of addiction; and researches in mental stimulation are hoped to provide answers and new solutions in this regard.

#### **1. Lack of causal models regarding the role of different brain areas and cognitive processes in addictive behaviour:**

One of the major limitations in the field of cognitive neuroscience is the use of correlation coefficients between external phenomena or cognitive processes with structural or functional indices in brain images or other biomarkers instead of determining causal relationships. For instance, it is known that the activation of different brain areas in functional brain imaging procedures such as fMRI is correlated with the feeling of drug craving. However, the causal role of each of these areas in generating the feeling of craving or act of drug seeking is hypothesized based on researchers' theorizing rather than direct findings of studies. Lesion studies are one of the rare chances to reach to a more causal model, but are almost impossible in human subjects, except having the chance to find cerebral infarction or localized traumatic brain injury cases. Using reversible non invasive brain stimulation methods in human subjects for the omission of the effect of a particular brain area or making a "virtual lesion" in the course of a specific cognitive process, it is now hoped that relevant causal relationships could be determined.

#### **2. The lack of objective instruments for the precise measurement of drug abuse related indices in patients, and determining the individualized difference between patients as well as assessment of the efficiency of therapeutic interventions:**

In the field of addiction studies, different instruments are used for assessment. Genetic indices, blood biomarkers, brain structural and functional changes, behavioural and cognitive functions, changes in physical and clinical conditions, and finally a vast range of subjective feelings and inferences are measured through biochemical tests, brain imaging, cognitive

and behavioural experiments, clinical examination, and self-report inventories, respectively. However, despite the employment of all the mentioned instruments, the subtle changes in chemical molecules at synapses, which could lead to the formation of specific explicit or implicit mental processes such as “craving” are not measurable except in particular circumstances and using complex radioisotope imaging techniques (PET). Therefore, researchers should inevitably make use of self-report questionnaires or indirect behavioural or cognitive tasks in this area. The questionnaires and clinical checklists are commonly used to determine the degree of feelings due to abuse of or abstinence from substances, such as craving, withdrawal, feeling high or intoxicated and etc. Also, the assessment of individuals at different stages of addiction such as individuals naive to drugs but prone to abuse, abusers, non-treatment seeker patients, and treatment-seeking patients, is also carried out through history taking and self report. Despite this vast application, the use of self report in the area of addiction is complicated with several limitations. The lack of response reliability as well as impaired personal insight and self awareness, renders the validity of the results problematic.

Studies carried out on the use of Single and Paired Pulse TMS for assessing the amount of brain excitability as well as the evaluation of speed of signal transfer (action potential conductance time) in intra and extra cerebral fibers between different nervous system locations, that are mainly dependent to certain neurochemical agents, has raised the prospects for finding more objective standards to detect chemical changes, that are in-charge for subjective feelings or implicit cognitive processing such as craving, at different levels of nervous system synapses in different states.

Individual differences in treatment responsiveness based on genetic polymorphism in proteins involved in synaptic transmission could be another focus point for using cortical excitability and signal transfer measures for improving patient selection and prediction of treatment outcome for neurochemical interventions.

### **3. Lack of effective and standard methods of biological intervention for the management of dependency on various psychotropic substances such as methamphetamine:**

Due to limitations of pharmacological methods with navigable effects on local changes caused by the abuse of addictive substances, efficient medications for many types of chemical dependencies are yet to be found. The significant strength of brain stimulating interventions in producing relatively stable local changes in the function of cerebral structures has brought about new optimism regarding the discovery of novel treatments using the present knowledge in this field. Positive therapeutic effects in psychiatric disorders such as depression, obsession, schizophrenia, and neurologic disorders such as vertigo, migraine headaches, cerebrovascular accidents, etc. which were introduced in recent years, has brought hope in this regard more than ever. Considering brain stimulation as an adjunctive treatment modality to improve current effective treatment protocols or a treatment option for non responsive cases to conventional interventions could be considered in

drug addictions receiving partially effective psychopharmacological treatments such as heroin addiction.

### **4. Lack of therapeutic interventions for the improvement of comorbid psychiatric illnesses in patients abusing psychotropic substances:**

Psychiatric comorbidities present in patients with substance abuse, such as depression and anxiety, are one of the major causes of treatment failure. Considering the complexities of the illness of addiction, managing these comorbidities via drugs, along with addiction specific pharmacotherapies, is very complicated and at times ineffective. Brain stimulation interventions could provide efficient answers to this problem in the field of addiction medicine.

Finally, we have to mention that we are not looking for a new miracle in neuroscience out of Non Invasive Brain Stimulation Technology (NIBS)!; But, published studies on NIBS are opening new horizons of hopes in this field especially from interventional point of view. I think addiction as a main national health concern and NIBS as a newly introduced method in neuroscience could be a good cross for neuroscientists in a developing country such as Iran as an initiative to joint to the global rapid movement to implement neuroscience in society. Brain stimulation division of Neurocognitive Laboratory in Iranian National Center for Addiction Studies as the first national comprehensive image guided NIBS academic Laboratory is trying to gather other colleagues' cooperation in this field to build up a new domain in neuroscience in the country trying to go toward answers of above mentioned questions. (We are sure that for a better understanding of “addiction” the use of more effective prevention and intervention measures are prospective and multimodal approaches to research are of central importance). The connection between the phenomenology and the underlying genetic or neurobiological processes allow first the identification of multifactorial causes and therefore the explanation of possible causalities. In addition, knowledge of neurobiological mechanisms will be contributing to the improvement and quality assurance of existing therapies and relapse prevention interventions. These efforts permit the establishment of a “research platform” on drug addiction and other related behavioural disorders, to discuss methods and strategies in order to promote faster progress and new findings.

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